ENVIRONMENTAL HEALTH PERSPECTIVES

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http://dx.doi.org/10.1289/ehp.1408258

Received: 10 February 2014

Accepted: 25 July 2014

Advance Publication: 29 July 2014

National Institute of Environmental Health Sciences

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Running title: BPA exposure and childhood obesity

Acknowledgments: This work was supported by NIEHS grants R00 ES020346, PO1 ES11261, R01 ES014575, and R01 ES020349. SAV was supported by Canadian Institutes of Health Research (CIHR) grant #12301 and Michael Smith Foundation for Health Research (MSFHR) grant #5176. We would like to acknowledge Christine Pfeiffer and Zia Fazili from the Centers for Disease Control and Prevention who performed the whole blood folate assays, as well as other laboratory staff who performed chemical analyses.

Disclosure: Dr. Lanphear has served as an expert witness and a consultant to the California Attorney General's Office for the plaintiffs in a public nuisance case related to childhood lead poisoning, but he has not personally received any compensation for these services. Dr. Lanphear has also served as a paid consultant on a US Environmental Protection Agency research study related to childhood lead poisoning. Dr. Braun was financially compensated for conducting a re-analysis of a study of child lead exposure for the plaintiffs in a public nuisance case related to childhood lead poisoning. None of these activities are directly related to the present study.

Competing Financial Interests: The authors do not have any actual or potential competing financial interests to declare.

Abstract

Background: Early life bisphenol A (BPA) exposure may increase childhood obesity risk, but few prospective epidemiological studies have investigated this relationship.

Objective: To determine if early life BPA exposure was associated with increased body mass index (BMI) at 2-5 years of age in 297 mother-child pairs from Cincinnati, OH (HOME Study).

Methods: Urinary BPA concentrations were measured in samples collected from pregnant women during the 2nd and 3rd trimesters and their children at 1 and 2 years of age. BMI z-scores were calculated from weight/height measures conducted annually from 2-5 years of age. We used linear mixed models to estimate BMI differences or trajectories with increasing creatinine-normalized BPA concentrations.

Results: After confounder adjustment, each 10-fold increase in prenatal (β = -0.1, 95% confidence interval [CI]: -0.5, 0.3) or early childhood (β = -0.2, CI: -0.6, 0.1) BPA concentrations was associated with a modest and non-significant reduction in child BMI. These inverse associations were suggestively stronger in girls compared to boys (prenatal effect measure modification [EMM] p-value = 0.30, early childhood EMM p-value = 0.05), but sex-specific associations were imprecise. Children in the highest early childhood BPA tercile had lower BMI at 2 years (difference = -0.3; CI: -0.6, 0) and larger increases in their BMI slope from 2-5 years (BMI increase per year = 0.12; CI: 0.07, 0.18) than children in the lowest tercile (BMI increase per year = 0.07; CI: 0.01, 0.13). All associations were attenuated without creatinine-normalization.

Conclusions: Prenatal and early childhood BPA exposures were not associated with increased BMI at 2-5 years, but higher early childhood BPA exposures were associated with accelerated growth during this period.

Introduction

Child obesity is one of the greatest public health challenges worldwide (WHO 2010). Excess food consumption and inadequate physical activity are major risk factors for obesity, but emerging evidence suggests that exposure to obesogens - chemicals that alter adipogenesis or metabolism – might play a role in increasing obesity risk beyond these traditional risk factors (Janesick and Blumberg 2012; Romano et al. 2014; Tang-Peronard et al. 2011). The developing fetus and infant may be especially sensitive to obesogens because of their immature detoxification pathways and sensitivity to environment inputs. Most epidemiological studies of environmental chemical obesogens have been limited to organochlorine compounds; few have examined contemporary chemicals, such as bisphenol A (BPA) (Tang-Peronard et al. 2011).

BPA is a high production volume chemical used to produce polycarbonate plastics and resins, and there is ubiquitous exposure among persons in industrialized countries (Braun et al. 2012; Lee et al. 2014; Quiros-Alcala et al. 2013; Valvi et al. 2013). BPA is a suspected endocrine disruptor and may affect the metabolism or action of hormones or receptors involved in the etiology of obesity, including glucocorticoids, gonadal hormones, and peroxisome proliferator activated receptors (Janesick and Blumberg 2012; Ross and Desai 2013). One animal study suggests that the obesogenic effect of BPA may by modified by the availability of methyl donors (e.g., folate) for DNA methylation, thus permanently altering the programming of adipogenesis, appetite, or energy metabolism, and increasing later-life obesity risk (Dolinoy et al. 2007).

While some animal studies suggest that BPA is a candidate obesogen, others do not (reviewed by Harley et al. 2013). Cross-sectional human studies suggest that urinary BPA concentrations are associated with increased body mass index (BMI) or obesity in adults and children, but these findings could result from confounding or reverse causation because diet is an important source of BPA exposure and obesity is linked to certain dietary patterns (Carwile and Michels 2011; Sharpe and Drake 2013; Trasande et al. 2012; Wang et al. 2012). Two prospective cohort studies examining early life BPA exposure report contradictory findings; one found higher BMI among children with higher prenatal BPA exposure and another reported lower BMI with higher prenatal exposure (Harley et al. 2013; Valvi et al. 2013). These studies suggest that girls may be more susceptible to prenatal BPA exposure, as well as children born to women who smoke during pregnancy.

We investigated whether prenatal or early childhood BPA exposure was associated with BMI or waist circumference in 2-5 year old children from a population-based, prospective cohort study conducted in Cincinnati, OH. We also determined if the association between prenatal BPA exposure and child BMI was modified by maternal folate levels, child sex, or prenatal tobacco smoke exposure.

Methods

Study participants

We used data from the Health Outcomes and Measures of the Environment (HOME) Study, a prospective cohort study designed to examine the health impact of early life exposure to prevalent environmental chemicals (Dietrich et al. 2005). We recruited pregnant women from nine prenatal clinics associated with three hospitals in the Cincinnati, Ohio area from March 2003 to January 2006. Eligibility criteria and enrollment have been previously described (Braun et al. 2009). All women provided written informed consent for themselves and their children after the study protocols had been explained. The institutional review boards of Cincinnati Children’s Hospital Medical Center, the cooperating delivery hospitals, and the Centers for Disease Control and Prevention (CDC) approved this study.

Maternal and child BPA exposure assessment

Because there is concern that BPA exposures may adversely affect child health depending on the timing of exposure, we examined exposures during two distinct periods of development – prenatal and early childhood. Women provided up to two spot urine samples in polypropylene cups at their prenatal care clinic visits around 16 and 26 weeks of pregnancy. Children provided up to two spot urine samples at annual clinic or home visits around 1 and 2 years of age (see Supplemental Material, Table S1 for mean and ranges). If a child did not provide a sample at the 1 or 2 year clinic visits, we used urine samples collected during home visits. Prior to urine collection, each child's genital area was wiped with a Wet Nap by their caregiver. For children who were not toilet trained, we placed a surgical insert into a clean diaper at the beginning of the study visit and checked the diaper for urine at the end of the study visit. If the diaper was wet and free of stool, the insert was placed into a polyethylene urine collection cup, and urine was expressed from the insert with a syringe. For children who were in the process of being toilet trained, a training toilet was lined with inserts. For toilet trained children, urine samples were collected directly into a urine collection cup with the aid of the child's caregiver. All samples were refrigerated until they were processed, after which they were stored at or below -20^{o}C until shipped on dry ice to CDC for analysis. BPA concentrations were measured at the CDC National Center for Environmental Health laboratories using previously described analytic chemistry methods (Ye et al. 2008). In 2009, we found non-detectable (< 0.4 ng/mL) levels of BPA in surgical inserts and wipes used to collect child urine.

To account for urine dilution, urinary creatinine (Cr) was measured by a kinetic Jaffe reaction, and BPA concentrations were divided by creatinine and multiplied by 100 to yield units of μg BPA/g Cr.

We averaged $\log_{10}$-transformed maternal and child creatinine-normalized BPA concentrations to create prenatal and early childhood BPA exposure measures, respectively. The prenatal exposure measure used maternal urinary BPA concentrations at 16 and 26 weeks gestation (7 had one measure and 290 had two measures). The early childhood exposure measure used child urinary BPA concentrations at 1 and 2 years of age (90 had one measure and 195 had two measures). We characterized creatinine-normalized urinary BPA concentrations as terciles or continuous $\log_{10}$-transformed values in our statistical models.

Child anthropometry

Weight, height, and waist circumference were averaged from three measurements taken in our study clinic. Weight at 2-5 years was obtained to the nearest 0.01 kg with the child dressed in undergarments or a dry diaper using a ScaleTronix scale (White Plains, NY). If the child was uncooperative, we obtained a sitting weight using a ScaleTronix Pediatric Scale Model 4802. Height at 2-5 years was measured to the nearest 0.1 cm using an Ayrton Stadiometer Model S100 with the child standing straight without shoes or head coverings and heels positioned against the wall. If the child had a hair style that prevented the child's head from laying flush against the head board, the height of the hairstyle was subtracted from the height measure. Waist circumference was measured at 4 and 5 years of age by placing a plastic measuring tape around a horizontal plane defined by the left and right iliac crests. Child BMI was converted to age- and sex-specific z-scores using United States references available from the National Center for Health Statistics (Kuczmarski et al. 2000). Research staff who conducted anthropometric measures were blinded to children's urinary BPA concentrations.

Confounding variables

We considered adjusting for potential confounders that might be associated with both BPA exposure and growth/size. Trained research assistants collected sociodemographic, perinatal, and dietary/activity variables using standardized computer-assisted interviews and medical chart reviews. Sociodemographic covariates included maternal race, age, education, marital status, household income, insurance status, and food security during pregnancy. Perinatal variables included maternal depressive symptoms at 16 weeks gestation (Beck Depression Inventory-II) (Beck et al. 1996), BMI at 16 weeks gestation, parity, and serum cotinine (a sensitive and specific biomarker of tobacco smoke exposure) (Braun et al. 2010).

Our dietary questions were originally designed to assess environmental chemical exposures (e.g., organophosphate pesticides), not macro- or micronutrient intake. We adjusted for frequency of maternal or child canned vegetable and fresh fruit/vegetable consumption since we previously found that canned vegetable consumption was associated with higher maternal urinary BPA concentrations and may be associated with diet quality (Braun et al. 2011). Dietary variables were collected during pregnancy for mothers and annually at 2-5 years of age for children. We adjusted for prenatal vitamin use and breast feeding duration because vitamins may be a source of methyl donors and breast feeding may decrease child obesity risk, respectively (Anderson et al. 2012; Lefebvre and John 2013). Child activity variables were collected annually at 2-5 years of age and included parent-reported hours of daily television watching and outdoor time.

We created unadjusted and several sets of adjusted models to verify the robustness of our results to potential confounding and selection bias. We created a primary model adjusting for sociodemographic and perinatal variables, and then additionally adjusted for maternal nutrition, child nutrition, child activity, child age, or maternal/child urinary di-2-ethylhexyl phthalate

(DEHP) metabolite concentrations. Urinary DEHP concentrations were measured using previously described methods (Silva et al. 2007). We also adjusted for both prenatal and early childhood urinary BPA concentrations simultaneously in the same model.

Statistical analyses

We began by describing the univariate characteristics of urinary BPA concentrations and calculating Pearson correlation coefficients between $\log_{10}$-transformed concentrations. Next, we calculated the mean BMI z-score at each age, as well as the number and percent of children with BMI z-scores ≥ the 85^{th} percentile (overweight). We then tabulated the mean BMI z-scores and median urinary BPA concentrations according to covariates.

We examined whether higher prenatal or early childhood BPA concentrations were associated with differences in BMI z-scores at 2-5 years or waist circumference at 4 and 5 years using a linear mixed model with an unstructured correlation matrix, random intercept, and empirical standard errors. This model accounts for the repeated and correlated measurements within an individual and increases our statistical precision by borrowing information across repeated measures (Fitzmaurice et al. 2004). The unstructured covariance matrix produced the best model fit according to the Akaike Information Criteria compared to compound symmetric or autoregressive covariance matrices. The coefficients from this model can be interpreted as the mean difference in BMI z-score averaged across 2-5 years of age with increasing BPA concentrations.

Then we used this same model to examine children's BMI z-score slopes between 2 and 5 years of age according to BPA concentration terciles. We modeled BMI z-scores as a function of BPA tercile, child age in months, an interaction term between age and BPA tercile, and covariates. This model allows each BPA tercile to have its own linear BMI z-score slope over time (i.e., 2-5 years of age). We then estimated the BMI slope per year for each BPA tercile and determined if these slopes were statistically different from one another using the age x BPA interaction terms.

We calculated the odds of being overweight (BMI z-score ≥ 85th percentile) according to BPA concentration using generalized linear mixed models with an unstructured correlation matrix and random intercept. Finally, we examined if the associations between BPA concentrations and BMI differed in boys and girls.

Secondary analyses

Based on prior studies examining prenatal BPA or other environmental chemical exposures and infant/child growth, we examined whether the association between prenatal urinary BPA concentrations and BMI was modified by prenatal tobacco smoke exposure, prenatal whole blood folate levels, and maternal race using product effect measure modification (EMM) terms (Dolinoy et al. 2007; Rauch et al. 2012; Valvi et al. 2013). We classified women as smokers if they had serum cotinine levels ≥ 3 ng/mL at 16 or 26 weeks gestation or birth; otherwise they were classified as non-smokers (Benowitz et al. 2009). Whole blood folate levels were measured in samples collected at 16 weeks gestation using previously described methods (Fazili and Pfeiffer 2004). We classified women into terciles based on the distribution of whole blood folate concentrations (34-387, 392-597, and 599-1,660 nmol/L). We only examined whites and blacks when examining EMM by race given the small sample size in 'Other Race' group.

We also conducted analyses excluding infants born small for gestational age (weight for gestational age < 10th percentile), women with gestational diabetes or hypertension, and one woman with a 26 week BPA concentration ~600-times higher than the median BPA concentration to determine if including these participants unduly influenced our results (Sathyanarayana et al. 2011). We re-ran our primary analyses without creatinine-normalizing urinary BPA concentrations. Finally, we examined the cross-sectional associations between children's urinary BPA concentrations and BMI at 2-5 years of age. Urinary BPA concentrations were measured in urine samples collected at 3, 4, and 5 years of age using the above described methods.

Results

Of 389 women who gave birth to singleton infants, 297 (76%) who had complete prenatal exposure data and covariates returned to our study clinic at least once for a total of 889 study visits between 2-5 years of age (285 for early childhood exposure analyses, 73%, 864 visits).

Median urinary BPA concentrations were lower in women compared to their children (Figure 1, Table 1, and Supplemental Material, Table S2). Creatinine-normalized BPA concentrations at 16 and 26 weeks (Pearson $R = 0.09$) or 1 and 2 years (Pearson $R = 0.10$) were not correlated; however non-normalized concentrations were weakly correlated (Pearson $R \leq 0.3$, Supplemental Material, Table S3). Averaged creatinine-normalized maternal urinary BPA concentrations were not correlated with averaged children's concentrations (Pearson $R = 0.03$, $p = 0.67$), but non-normalized concentrations were weakly correlated (Pearson $R = 0.17$, $p < 0.01$).

Children's BMI z-scores ranged from a mean of 0 to 0.2 standard deviation scores (SDS) between 2 and 5 years of age; 16-19% of children had BMI z-scores ≥ the 85th percentile (Supplemental Material, Figure S1).

Higher prenatal urinary BPA concentrations were observed in mothers who were black, younger at delivery, had less household income and education, consumed more canned vegetables and less fresh fruits and vegetables, or breastfed for a shorter duration (Table 1). Similar patterns were observed for early childhood urinary BPA concentrations.

After confounder adjustment, higher prenatal or early childhood urinary BPA concentrations were not associated with BMI z-scores in children at 2-5 years of age (Table 2). Results were similar regardless of adjustment for dietary/activity factors, child age, or both BPA exposures (Supplemental Material, Table S4). Not normalizing BPA concentrations for creatinine attenuated both the prenatal and early childhood estimates to null (Supplemental Material, Table S5). Both prenatal and early childhood urinary BPA concentrations were associated with smaller waist circumference at 4 and 5 years of age, but the 95% confidence intervals (CI) of the point estimates included the null value (Supplemental Material, Table S6).

Inverse associations between maternal urinary BPA concentrations and child BMI were slightly stronger among girls ($\beta = -0.4$; CI: -0.9, 0.2; n = 165) compared to boys ($\beta = 0.0$; CI: -0.5, 0.6; n = 132), although the EMM p-value did not reach conventional levels of significance (p-value = 0.30) (Figure 2). The evidence for EMM was stronger for early childhood urinary BPA concentrations (p-value=0.05), where higher concentrations were associated with lower child BMI among girls ($\beta = -0.6$; CI: -1.1, -0.1; n = 155) than boys ($\beta = 0.1$; CI: -0.4, 0.5; n = 130). The magnitude of the differences between the sexes was attenuated when BPA concentrations were not creatinine-normalized (Supplemental Material, Table S7).

Each 10-fold increase in maternal urinary BPA concentrations was associated with a modestly decreased odds of being overweight between 2 and 5 years of age (odds ratio [OR] = 0.65; CI: 0.19, 2.18, p = 0.48), but the OR CI included the null value. The association between early childhood urinary BPA concentrations and being overweight was much closer to null (OR = 0.93; CI: 0.34, 2.53, p = 0.89).

There was not strong evidence that maternal urinary BPA concentrations were positively associated with rapid growth between 2 and 5 years of age (Figure 3) (age x BPA interaction term p-value = 0.26). There was stronger evidence that BMI slopes increased more rapidly between 2 and 5 years among children in the highest tercile of early childhood BPA concentrations (BMI increase per year = 0.12; CI: 0.07, 0.18) compared to children in the 1st (BMI increase per year = 0.07; CI: 0.01, 0.13) or 2nd (BMI increase per year = 0.04; CI: -0.02, 0.11) terciles (age x BPA tercile interaction p-value = 0.14). This increase was coincident with lower BMI at 2 years of age among children in the 3rd tercile compared to children in the 1st tercile (BMI difference = -0.3; CI: -0.6, 0); while BMI differences were not evident at 5 years of age (BMI difference = -0.1; CI: -0.5, 0.2). BMI slopes no longer differed when early childhood BPA concentrations were not creatinine-normalized (1st tercile = 0.04; CI: -0.02, 0.10; 2nd tercile = 0.09; CI: 0.04, 0.15; 3rd tercile = 0.09; CI: 0.03, 0.15; p-value for interaction = 0.42).

There was not strong evidence that the associations between prenatal or early childhood BPA concentrations and BMI z-score slopes differed according to child sex (EMM p-values=0.18 to 0.80). However, we had a relatively small number of children for this analysis (Supplemental Material, Figures S2 and S3).

Secondary analyses

Associations between continuous prenatal urinary BPA concentrations and child BMI did not differ (EMM p-value = 0.98) among children born to mothers who smoked during pregnancy (β = -0.1; CI: -1.9, 1.6, n = 29) compared to those who did not smoke (β = -0.1; CI: -0.5, 0.3, n = 268). The associations between prenatal urinary BPA concentrations and child BMI did not differ according to terciles of maternal whole blood folate levels (EMM p-value=0.74). There was no evidence that associations between prenatal or early childhood urinary BPA concentrations and BMI differed in blacks or whites (EMM p-values > 0.34). Our results did not appreciably change when we adjusted for children's serum cotinine levels, adjusted for maternal or child urinary DEHP concentrations, or excluded infants born small for gestational age, women with gestational diabetes or pregnancy induced hypertension, or the woman with the exceptionally high BPA concentration (Supplemental Material, Table S5). The cross-sectional associations between children's concurrent urinary BPA concentrations and BMI z-scores at 2-5 years were both positive and negative in direction (Supplemental Material, Table S8).

Discussion

Prenatal urinary BPA concentrations were not associated with increased BMI or waist circumference in these preschool aged children. In fact, consistent with the results from a prospective birth cohort study in California, we found that higher maternal urinary BPA concentrations were generally, but not significantly, associated with lower BMI in girls. Harley et al. (2013) reported modest decreases in child BMI at 9 years of age among girls born to women with the highest prenatal urinary BPA concentrations.

Our findings and those of Harley et al. (2013) are not consistent with those from a prospective cohort in Spain. Valvi and colleagues (2013) found that maternal urinary BPA concentrations during pregnancy were associated with increased child BMI and waist circumference at 4 years of age. They also reported that these associations were stronger among women who smoked during their pregnancy, but did not find any differences by child sex. Maternal smoking did not modify the association between prenatal BPA concentrations and child BMI in our cohort, but the statistical power to detect this modification was limited by the relatively small number of smokers.

Early childhood urinary BPA concentrations were not associated with BMI or waist circumference at 2-5 years of age in this cohort and point estimates were negative in direction. In contrast, two cross-sectional studies, one from California and another using the National Health and Nutrition Examination Survey, observed positive associations between urinary BPA concentrations and BMI or percent body fat among school-age and adolescent children (Harley et al. 2013; Trasande et al. 2012). Consistent with our findings, the New England Children's Amalgam Trial, a randomized, prospective trial of dental amalgams and composite fillings did not find an association between childhood exposure to BPA-diglycidyl dimethacrylate composite dental fillings and increased child BMI or percent body fat (Maserejian et al. 2012).

With regard to the three prospective cohort studies (including the present study) with urinary BPA measurements; differences in study design, urinary BPA concentrations, or the timing of BMI measurements do not seem to explain the discrepancies in their results. All three cohorts measured urinary BPA concentrations twice during pregnancy and the two US studies measured children's BPA concentrations at the time BMI was assessed. Maternal urinary BPA concentrations were higher among women in this (median: 2.1 μg/L) and the Spanish (median: 2.1 μg/L) study than the California study (median: 1.1 μg/L) (Harley et al. 2013; Valvi et al. 2013). Child BMI was measured longitudinally at 2-5 years of age in this study, at 14 months and 4 years in the Spanish study, and at 9 years of age in the California study. Confounding, BPA exposure misclassification, differences in distributions of effect measure modifiers, incorrect model specification, or residual sources of selection bias may explain the discrepancies across epidemiological studies (Howe et al. 2011).

Positive associations between urinary BPA concentrations and BMI or percent body fat in cross-sectional analyses may be due to residual confounding from unmeasured dietary sources of BPA exposure that are also important determinants of adiposity (e.g., soda or canned foods). It has also been suggested that BPA may simply be a marker of certain dietary patterns associated with obesity (Sharpe and Drake 2013). However, this hypothesis bears further scrutiny in light of the known dietary sources of BPA and the effect of these foods on obesity or cardiometabolic disease risk. For instance, canned foods are a major source of BPA in adults (Carwile et al. 2011; von Goetz et al. 2010) and some canned foods contain high levels of fiber and other micronutrients (e.g., canned beans), while others may be less nutritious (e.g., canned pasta). Thus, the direction of confounding will depend on the dietary source of BPA exposure and its association with obesity. Traditional measures of dietary quality, like food frequency questionnaires, may misspecify dietary confounding because these measures are designed to assess macro- or micronutrient intake rather than contaminants present in the food. Thus, there is a need to develop and control for dietary quality measures that incorporate potential sources of BPA exposure.

One strength of our study was the ability to control for socioeconomic, perinatal, and environmental factors, including tobacco smoke and phthalate exposures. However, we had imperfect measures of maternal and child diet and physical activity. Our results were not substantially different when we controlled for these measures of diet or physical activity; however, the inability to adjust for more accurate diet and activity measures may have biased our results.

Associations between urinary BPA concentrations and BMI may be due to physiological changes during pregnancy or early childhood that affect BPA excretion and fetal/child growth. For instance, children with BMI trajectories that have an early BMI nadir are at an increased risk of obesity or overweight compared to children who grow normally (Williams and Goulding 2009). Children on different growth trajectories may have different BPA or creatinine excretion patterns before they develop obesity making it difficult to disentangle associations between urinary BPA concentrations and body composition from prodromal obesity-induced pharmacokinetic changes, even with prospective data. We speculate that this may be why the association between early childhood urinary BPA concentrations and child BMI was attenuated when we did not adjust for creatinine. While creatinine-normalization is commonly used to account for urine dilution, it may not be an ideal marker of urine dilution when examining obesity or body composition.

It is well-established that urinary BPA concentrations exhibit a high degree of within-person variability due to the relatively short biological half-life of BPA and the episodic nature of exposure (Braun et al. 2012; Teitelbaum et al. 2008; Volkel et al. 2002). This may lead to exposure misclassification, reduced statistical power for detecting potential associations, and null-attenuated effect estimates. This would substantially reduce our power to determine if sex, race, prenatal tobacco smoke exposure, or maternal folate levels modified the association between urinary BPA concentrations and BMI. This is evident from the wider confidence intervals for the sex-specific associations compared to the full-cohort associations.

Another strength of our study is that we had up to four serial urinary BPA measures, two during pregnancy and two during early childhood, but even this may be insufficient to accurately classify exposure over long time periods. In addition, BPA exposure during narrower time windows or at other times of development (e.g., first trimester) may be more important than the exposure windows we measured. Alternative methods and matrices of BPA exposure assessment should be considered in future studies. Collecting more spot urine samples may improve exposure assessment, but the number of samples needed to ensure reasonable exposure classification and the impact of collecting these additional specimens on participants' compliance is unknown. Other matrices that may have less within-person variability or reflect longer periods of exposure, like meconium or shed deciduous teeth should be considered and investigated when feasible.

We used up to four repeated BMI measures in children to quantify the association between early life BPA exposures and absolute differences in child BMI, as well as the BMI slope between 2 and 5 years. Repeated BMI measures will reduce misclassification of child adiposity. However, child BMI is related to both fat and lean mass, and may not be highly correlated with direct measures of adiposity, especially when a child's BMI is below the 85th percentile (Freedman et al. 2005). Other measures of body composition, including densitometry, bioelectric impedance, and dual energy X-ray absorptiometry can quantify fat and lean mass in separate body compartments to provide more accurate phenotyping of adipose distribution (Wells 2001). Future research should examine the relationship between BPA exposures and more refined body composition measures in children.

A prior rodent study found that dietary methyl donors (e.g., folic acid) might reduce obesity risk from prenatal BPA exposure (Dolinoy et al. 2007), but another did not (Rosenfeld et al. 2013). We did not find that the association between prenatal urinary BPA concentrations and child BMI differed according to maternal folate status. This may be due to differences in the timing of BPA or folate measurement in our study relative to dosing in animal studies, higher BPA exposure in animal studies compared to human exposures, or species-specific responses.

Prenatal and early childhood BPA exposures were not associated with increased child BMI at 2-5 years of age in this birth cohort. There was some evidence suggesting that higher early childhood BPA exposures were associated with faster BMI velocity, but this association was attenuated without creatinine adjustment. Further follow-up in this and larger cohort studies is warranted to assess whether prenatal or early childhood BPA exposure ultimately results in higher BMI at later ages. In addition, studies in larger cohorts are needed to quantify potential sex-specific associations. Future studies should develop and integrate more refined measures of nutrient intake that incorporate potential sources of BPA exposure and improve methods to assess BPA exposure.

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Table 1. Urinary BPA concentrations and child BMI z-scores according to maternal and child covariates among Cincinnati, OH women and their children.

Covariate	N	Median maternal BPA mg/L (25th, 75th)[a]	Median child BPA mg/L (25th, 75th)[b]	Mean BMI z-score ± SD[c]
Overall	297	2.1 (1.1, 3.9)	3.6 (1.8, 6.9)	0.04 ± 1.04
Maternal race				
White	198	1.7 (0.9, 2.9)	2.7 (1.5, 5.4)	0.03 ± 1.00
Black	82	3.9 (2.4, 6.3)	5.5 (3.4, 9.6)	0.10 ± 1.15
Other	17	2.3 (1.7, 3.2)	4.7 (2.6, 6.2)	-0.06 ± 1.00
Maternal age (years) at delivery				
< 25	58	3.5 (1.9, 6.2)	4.9 (2.5, 7.6)	0.05 ± 1.16
25 - < 35	192	1.9 (1.0, 3.7)	3.4 (1.6, 6.2)	0.04 ± 1.02
35+	47	1.7 (0.7, 3.2)	3.1 (1.7, 7.6)	0.04 ± 1.01
Maternal education				
Graduate/professional/bachelor	166	1.7 (0.8, 2.7)	2.6 (1.5, 5.3)	0.08 ± 0.90
Some college	74	2.8 (1.7, 4.8)	4.2 (2.6, 7.4)	-0.15 ± 1.08
High school	31	3.2 (2.1, 6.2)	4.9 (2.5, 7.1)	0.39 ± 1.04
< High school	26	6.1 (3.2, 7.5)	5.9 (3.5, 12.0)	-0.10 ± 1.56
Marital status				
Married	207	1.8 (0.9, 2.9)	2.9 (1.6, 5.8)	0.05 ± 1.01
Unmarried-living together	33	3.2 (2.2, 6.4)	4.2 (2.3, 7.3)	0.26 ± 1.00
Unmarried-living alone	57	3.7 (1.9, 6.3)	5.2 (3.5, 9.4)	-0.10 ± 1.16
Household income (per year)				
≥ $80,000	88	1.6 (0.8, 2.6)	2.9 (1.5, 5.3)	0.01 ± 0.87
$40,000-80,000	110	1.8 (0.9, 3.0)	2.7 (1.6, 5.7)	0.12 ± 1.10
$20,000-$40,000	41	2.9 (1.8, 4.5)	4.3 (2.9, 8.0)	-0.06 ± 1.14
< $20,000	58	5.1 (2.6, 7.5)	5.3 (3.2, 9.2)	0.01 ± 1.10
Maternal employment				
No	52	2.3 (1.4, 6.2)	3.9 (2.0, 8.2)	-0.07 ± 1.06
Yes	245	2.0 (1.0, 3.8)	3.4 (1.7, 6.7)	0.07 ± 1.04
Maternal insurance				
Private	226	1.8 (0.9, 3.0)	3.0 (1.6, 5.9)	0.06 ± 1.00
Public/none	71	4.3 (2.3, 6.9)	5.0 (3.1, 9.1)	-0.02 ± 1.15
Maternal depressive symptoms				
Minimal	245	2.0 (1.0, 3.8)	3.5 (1.8, 6.7)	-0.01 ± 1.02
Mild	32	2.8 (1.8, 6.3)	4.0 (1.7, 9.1)	0.21 ± 1.02
Moderate/severe	20	2.7 (1.3, 4.3)	3.7 (2.1, 7.0)	0.41 ± 1.25
Maternal serum cotinine concentration (ng/mL)				
Unexposed (< 0.015)	120	1.5 (0.8, 2.7)	2.7 (1.4, 6.2)	-0.04 ± 0.98
Secondhand (0.015-3)	150	2.7 (1.5, 4.4)	3.9 (2.3, 7.3)	0.09 ± 1.07
Active (≥ 3)	27	4.2 (2.3, 6.7)	3.7 (1.7, 6.2)	0.16 ± 1.14
Maternal BMI (kg/m^2)				
< 25	126	1.9 (1.0, 3.5)	3.4 (1.8, 7.1)	-0.14 ± 1.02
25 - < 30	101	1.7 (0.8, 3.2)	2.8 (1.7, 5.4)	0.05 ± 0.94
30+	70	3.4 (2.1, 6.2)	4.7 (2.3, 9.4)	0.35 ± 1.16

Covariate	N	Median maternal BPA mg/L (25th, 75th)[a]	Median child BPA mg/L (25th, 75th)[b]	Mean BMI z-score ± SD[c]
Parity				
0	128	1.8 (0.8, 3.7)	3.3 (1.6, 5.6)	0.03 ± 1.00
1	98	2.2 (1.4, 4.1)	3.7 (2.0, 7.3)	0.14 ± 0.99
2+	71	2.4 (1.5, 4.2)	4.0 (2.0, 8.2)	-0.07 ± 1.17
Prenatal vitamin use				
Never or few times/month	41	2.7 (1.8, 5.1)	4.5 (3.1, 8.2)	-0.02 ± 1.22
Daily or weekly	256	2.0 (1.0, 3.8)	3.4 (1.7, 6.3)	0.05 ± 1.01
Prenatal canned vegetable consumption frequency				
≤ Monthly	83	1.8 (0.8, 3.8)	3.3 (1.8, 5.6)	0.08 ± 0.90
Weekly	174	2.1 (1.2, 4.0)	3.5 (1.6, 6.7)	0.06 ± 1.07
≥ Daily	40	2.1 (1.4, 3.9)	5.4 (3.0, 9.3)	-0.13 ± 1.18
Prenatal fresh fruit and vegetable consumption frequency				
Monthly/weekly	175	2.4 (1.3, 4.2)	3.8 (2.0, 7.6)	0.03 ± 1.06
≥ Daily	122	1.8 (0.9, 3.5)	3.2 (1.6, 5.7)	0.05 ± 1.01
Breast feeding duration (months)				
None	49	2.8 (1.5, 6.0)	2.9 (1.8, 8.2)	-0.02 ± 1.19
> 0 to 3.25 months	83	2.9 (1.7, 4.8)	4.0 (2.3, 6.5)	0.10 ± 1.15
3.5 to 10.5 months	80	1.8 (0.9, 3.2)	3.2 (1.6, 6.2)	0.09 ± 0.95
> 10.5 months	85	1.9 (0.9, 3.0)	3.4 (1.8, 7.3)	-0.03 ± 0.93
Child canned vegetable consumption frequency				
≤ Monthly	47	1.9 (0.9, 3.5)	2.6 (1.5, 5.1)	0.14 ± 0.82
Weekly	192	2.1 (1.1, 3.9)	3.6 (1.8, 7.3)	0.03 ± 1.08
≥ Daily	49	2.3 (0.9, 3.9)	3.8 (2.3, 6.3)	-0.04 ± 1.07
Child fresh fruit and vegetable consumption frequency				
Monthly/weekly	149	2.6 (1.3, 4.3)	4.2 (2.1, 8.1)	-0.01 ± 1.07
≥ Daily	139	1.8 (0.9, 3.3)	2.7 (1.5, 5.2)	0.08 ± 1.01
Child daily TV watching				
< 1 hour	123	2.0 (1.0, 3.5)	3.4 (1.7, 5.6)	0.06 ± 0.99
1-2 hours	85	1.9 (1.0, 3.8)	3.1 (1.5, 7.8)	0.00 ± 1.09
> 2 hours	78	2.7 (1.5, 5.1)	4.0 (2.3, 7.5)	0.07 ± 1.07
Child daily outdoor time				
< 1 hour	204	2.2 (1.1, 4.1)	3.8 (1.8, 7.3)	0.07 ± 1.11
1-2 hours	44	2.0 (0.9, 3.8)	3.3 (1.6, 6.2)	-0.08 ± 0.88
> 2 hours	40	1.6 (0.9, 3.2)	2.9 (2.0, 4.6)	0.02 ± 0.82

[a]Average BPA concentration in maternal 16 and 26 week gestation urine samples (n = 297). [b]Average BPA concentration in child 1 and 2 year urine samples (n = 285). [c]BMI z-score at the child's first visit if more than one was available.

Table 2. Adjusted change in child BMI z-score between 2-5 years of age (beta) by tercile of or with a 10-fold increase in maternal or early childhood urinary BPA concentrations among Cincinnati, OH women and their children.[a]

BPA exposure measure	N	Mean BMI Z-score	Beta (CI)	p-value
Prenatal				
1st Tercile (0.4-1.6 mg/g Cr)	99	0.00	Ref	Ref
2nd Tercile (1.6-2.6 mg/g Cr)	99	-0.01	0.0 (-0.3, 0.3)	0.98
3rd Tercile (2.6-49 mg/g Cr)	99	0.05	0.1 (-0.2, 0.3)	0.66
Continuous, log_{10}-transformed	297		-0.1 (-0.5, 0.3)	0.51
Early childhood				
1st Tercile (2.1-11 mg/g Cr)	95	0.13	Ref	Ref
2nd Tercile (11-20 mg/g Cr)	95	0.12	0.0 (-0.3, 0.3)	0.96
3rd Tercile (20-314 mg/g Cr)	95	-0.10	-0.2 (-0.5, 0.1)	0.12
Continuous, log_{10}-transformed	285		-0.2 (-0.6, 0.1)	0.19

[a]Maternal race (white, black, and other), marital status (married living together, unmarried living together, and unmarried living alone), parity (0, 1, and 2+), age at delivery (continuous in years), household income (continuous in $10,000 increments), education (< high school, high school, some college, and ≥ bachelor's degree), employment (any and none), insurance (private and public/none), BMI at 16 weeks (continuous in kg/m^2), depressive symptoms at baseline (continuous), and prenatal serum cotinine (continuous, log_1-transformed).

Figure legends

Figure 1. Urinary BPA concentrations during pregnancy and the 1st 2 years of life among Cincinnati, OH women and their children. Whiskers represent the minimum and maximum, box edges represent the 25th and 75th percentiles, line in box represents the median, and diamond represents the arithmetic mean. Number of mothers/children for the average concentrations is greater than the individual concentrations since not all the same participants returned at the both visits.

Figure 2. Adjusted change in child BMI z-score between 2-5 years of with a 10-fold increase in maternal or early childhood urinary BPA concentrations among Cincinnati, OH women and their children-Stratified by child sex. Adjusted for maternal race (white, black, and other), marital status (married living together, unmarried living together, and unmarried living alone), parity (0, 1, and 2+), age at delivery (continuous in years), household income (continuous in $10,000 increments), education (< high school, high school, some college, and ≥ bachelor's degree), employment (any and none), insurance (private and public/none), BMI at 16 weeks (continuous in kg/m^2), depressive symptoms at baseline (continuous), and prenatal serum cotinine (continuous, log$_{10}$-transformed). Prenatal effect measure modification p-values: With creatinine: 0.30, No creatinine: 0.39. Early childhood effect measure modification p-values: With creatinine: 0.05; No creatinine: 0.06. Error bars represent 95% confidence limits.

Figure 3. Adjusted BMI z-scores slopes between 2 and 5 years of age by prenatal and early childhood BPA tercile among Cincinnati, OH women and their children. Adjusted for maternal race (white, black, and other), marital status (married living together, unmarried living together, and unmarried living alone), parity (0, 1, and 2+), age at delivery (continuous in years), household income (continuous in $10,000 increments), education (< high school, high school,

some college, and ≥ bachelor's degree), employment (any and none), insurance (private and public/none), BMI at 16 weeks (continuous in kg/m^2), depressive symptoms at baseline (continuous), and prenatal serum cotinine (continuous, $\log_{10}$-transformed). Prenatal BPA x age interaction p-values: 2nd vs. 1st tercile: 0.42, 3rd vs. 1st tercile: 0.43. Early childhood BPA x age interaction p-values: 2nd vs. 1st tercile: 0.51, 3rd vs. 1st tercile: 0.22. Prenatal BPA Terciles: 1st Tercile: 0.4-1.6 μg/g Cr, 2nd Tercile: 1.6-2.6 μg/g Cr, and 3rd Tercile: 2.6-49 μg/g Cr. Early Childhood BPA Terciles: 1st Tercile: 2.1-11 μg/g Cr, 2nd Tercile: 11-20 μg/g Cr, and 3rd Tercile: 20-314 μg/g Cr.

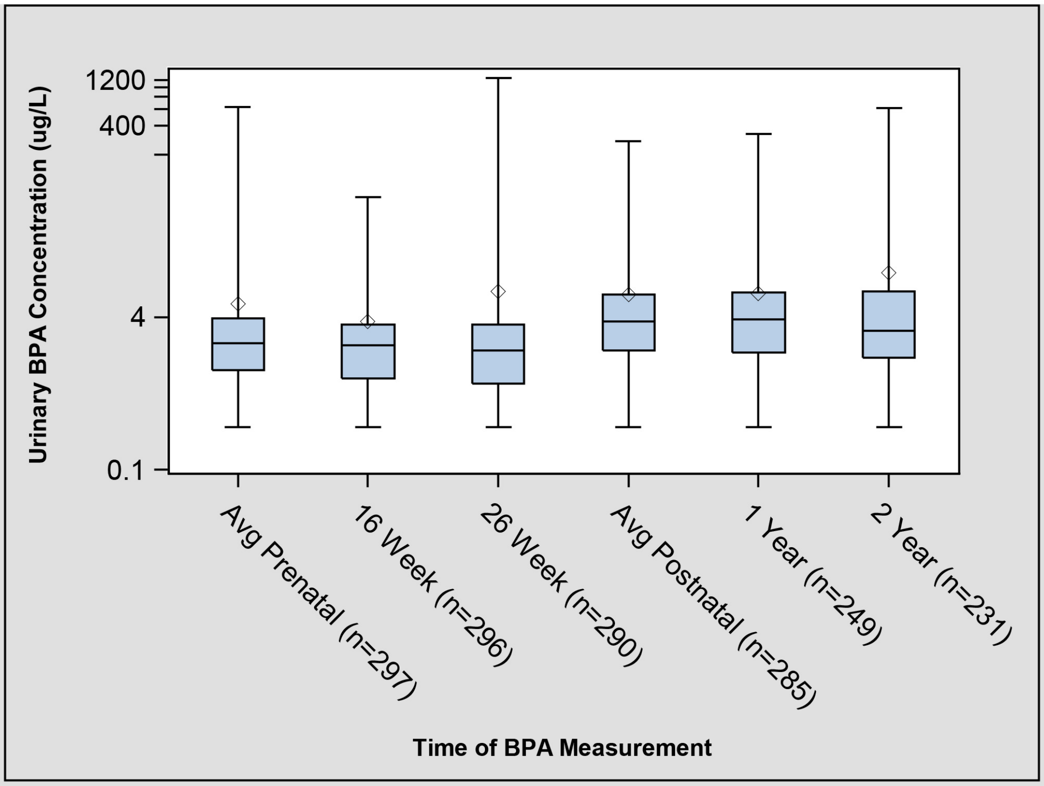
Urinary BPA Concentration (ug/L)
1200
400
4
0.1
Avg Prenatal (n=297)
16 Week (n=296)
26 Week (n=290)
Avg Postnatal (n=285)
1 Year (n=249)
2 Year (n=231)
Time of BPA Measurement

Figure 1

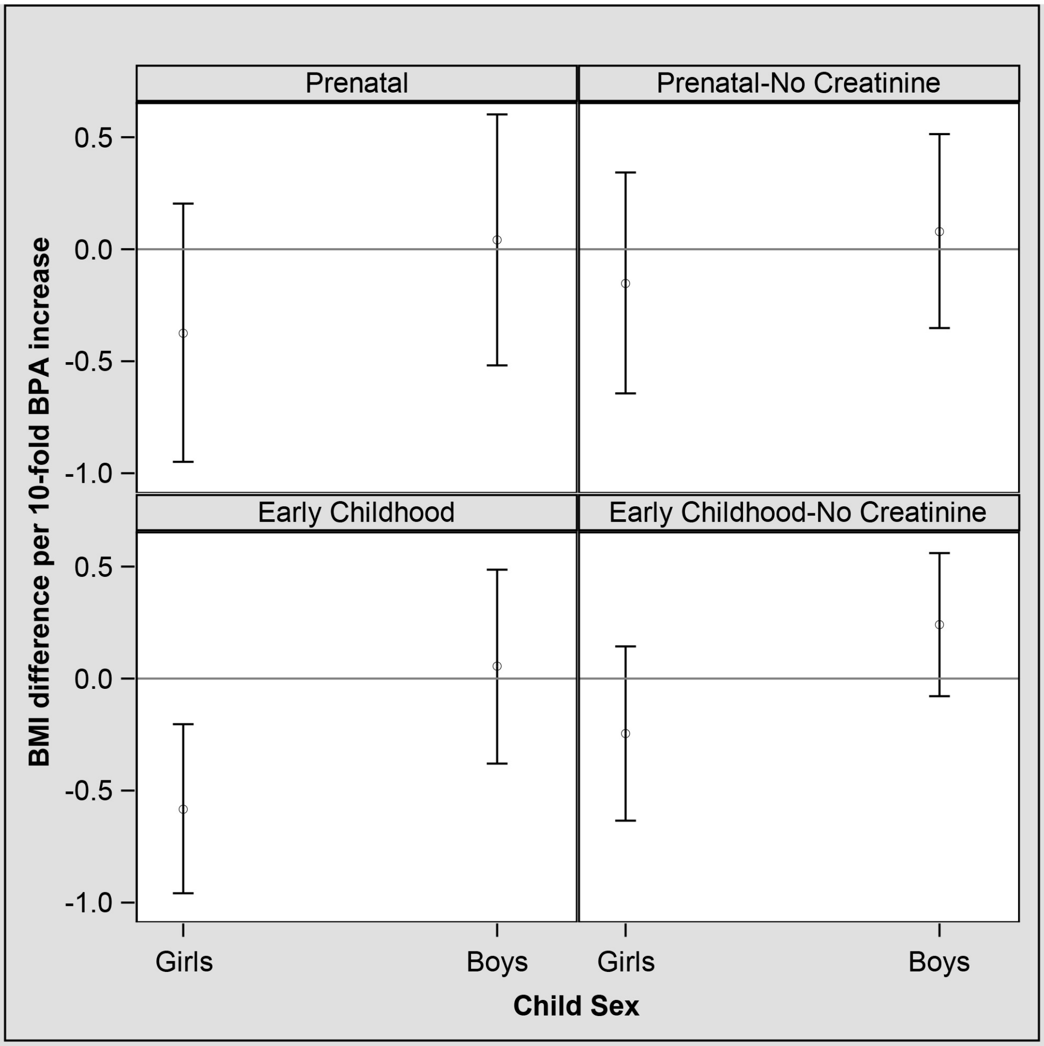
Prenatal
Prenatal-No Creatinine
Early Childhood
Early Childhood-No Creatinine
BMI difference per 10-fold BPA increase
0.5
0.0
-0.5
-1.0
Girls
Boys
Child Sex

Figure 2

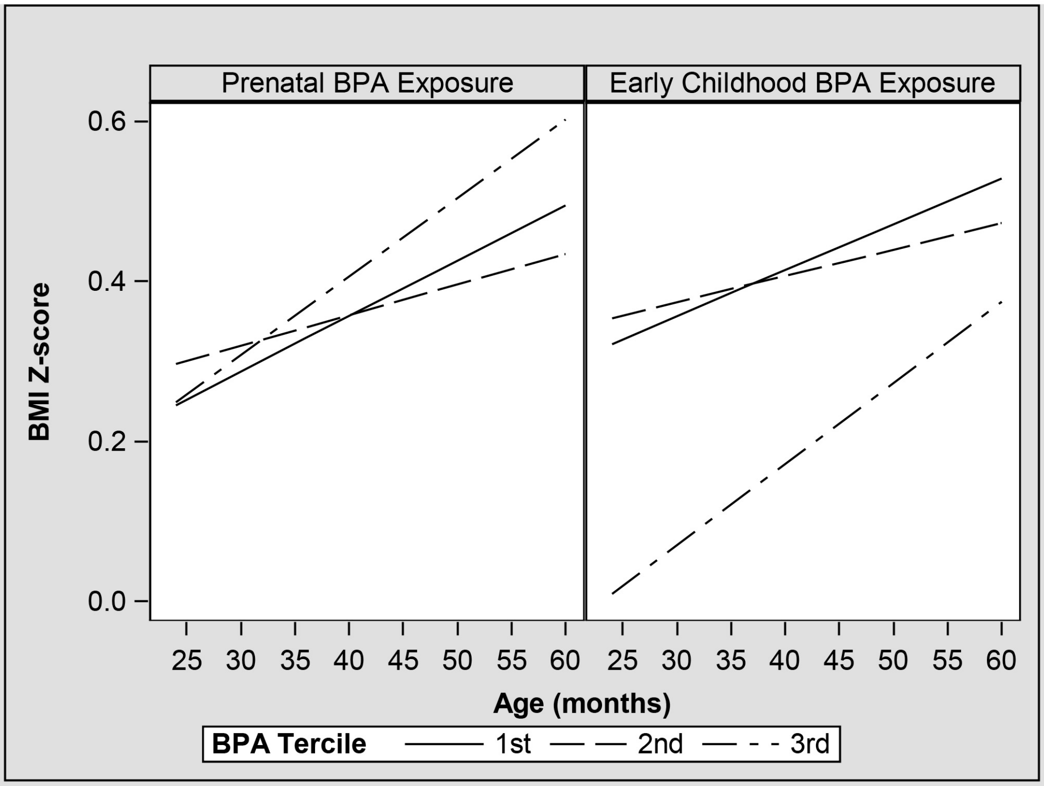
Prenatal BPA Exposure
Early Childhood BPA Exposure
0.6
0.4
0.2
0.0
BMI Z-score
25 30 35 40 45 50 55 60 25 30 35 40 45 50 55 60
Age (months)
BPA Tercile 1st 2nd 3rd

Figure 3